

# Future of Cannabis and Cannabinoids in Therapeutics

Ethan Russo

**SUMMARY.** This study reviews human clinical experience to date with several synthetic cannabinoids, including nabilone, levonantradol, ajulemic acid (CT3), dexamabinol (HU-211), HU-308, and SR141716 (Rimonabant®). Additionally, the concept of “clinical endogenous cannabinoid deficiency” is explored as a possible factor in migraine, idiopathic bowel disease, fibromyalgia and other clinical pain states. The concept of analgesic synergy of cannabinoids and opioids is addressed. A cannabinoid-mediated improvement in night vision at the retinal level is discussed, as well as its potential application to treatment of retinitis pigmentosa and other conditions. Additionally noted is the role of cannabinoid treatment in neuroprotection and its application to closed head injury, cerebrovascular accidents, and CNS degenerative diseases including Alzheimer, Huntington, Parkinson diseases and ALS.

Excellent clinical results employing cannabis based medicine extracts (CBME) in spasticity and spasms of MS suggests extension of such treatment to other spasmodic and dystonic conditions.

Finally, controversial areas of cannabinoid treatment in obstetrics, gynecology and pediatrics are addressed along with a rationale for such interventions. [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <<http://www.HaworthPress.com>> © 2003 by The Haworth Press, Inc. All rights reserved.]

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### *INTRODUCTION*

As is evident from preceding information in this publication, an increasingly bright future seems to be on the horizon for cannabis therapeutics, whether herbally-based or designed to utilize its various components. The pros and cons of cannabis proper, whether smoked, ingested orally, or vaporized have been previously addressed. A wide variety of delivery systems is possible in the future. The present selection will detail additional preparations, particularly synthetic cannabinoids, and discuss how they and cannabis-based pharmaceuticals may be applied in future clinical therapeutics.

### *NABILONE*

Nabilone is a synthetic cannabinoid, pharmacologically similar to THC, but with higher potency, a lesser likelihood to produce euphoria, and displaying a lower “abuse potential” (Association 1997). It is manufactured by Eli Lilly Company as Cesamet® and is available in the UK, Australia, Canada, and some European nations (Grotenhermen 2001), where it is primarily utilized as an anti-nausea agent in chemotherapy. Occasional reports have claimed benefit on spasticity in multiple sclerosis and dyskinesias. Lethal reactions have occurred in chronic canine usage (Mechoulam and Feigenbaum 1987).

Analgesic effects of nabilone in neuropathic pain patients have been noted (Notcutt, Price, and Chapman 1997), but prominent adverse effects included drowsiness and dysphoria. Some patients stated a clear preference for smoked cannabis in terms of side effects and analgesic efficacy. Nabilone’s cost was estimated to be 10 times higher than herbal cannabis at black market rates, and all things considered, this agent would seem to have more disadvantages in the long term.

### *LEVONANTRADOL*

Levonantradol is another synthetic cannabinoid from Pfizer. Analgesic benefits of up to 6 hours were noted in post-operative pain patients in

a prior trial (Jain et al. 1981), but without clear dose-response effects. Adverse effects are prominent with this agent, including somnolence in 50-100% and dysphoria in 30-50% (Association 1997), termed “unacceptable” by that authority.

### ***AJULEMIC ACID (CT3)***

Ajulemic acid is a synthetic cannabinoid derived from the more stable THC-11-oic acid that does not bind to CB<sub>1</sub> receptors and lacks psychoactive effects. It is currently in commercial development. It has shown strong analgesic and anti-inflammatory properties in animal models of arthritis without COX-1 inhibition side effects such as ulcer production, and is advanced clinical trials (Burstein 2001, 2000). It shares anti-neoplastic effects with THC on a variety of cell lines (Recht et al. 2001), but is half as potent in this regard, although longer acting. Ajulemic acid has recently been demonstrated to bind to the peroxisome proliferator-activated receptor gamma, part of the nuclear receptor superfamily involved in inflammatory processes (Liu et al. 2003), and also to suppress human monocyte interleukin-1beta production *in vitro* (Zurier et al. 2003). Ajulemic acid portends to be a valuable addition to the pantheon of cannabinoid pharmaceuticals employed for analgesic and anti-inflammatory properties.

### ***DEXANABINOL (HU-211)***

Dexanabinol is a synthetic cannabinoid agent developed at Hebrew University from  $\Delta^8$ -THC, but it is a non-psychoactive enantiomer of the fabulously potent HU-210 (Pop 2000). It has demonstrated numerous interesting properties including antioxidant and anti-inflammatory effects, as well as suppression of THF-alpha (tumor necrosis factor) production. Additionally, it reduced brain damage associated with soman (Sarin)-induced seizures in rats (Filbert et al. 1999), caused reduction of experimental autoimmune encephalomyelitis responses (Achiron et al. 2000) suggesting application in multiple sclerosis, and reduced damage in experimental focal ischemia (Lavie et al. 2001). Human trials have demonstrated mixed results. In one such Phase II study of 67 closed head injury patients, dexanabinol reduced intracranial pressure and perfusion significantly with a good adverse effect profile (Knoller et al.

2002), with some degree of improvement in clinical outcome scales after 3 and 6 months.

Dexanabinol is currently in Phase III clinical trials, and further analysis will demonstrate its relative place in the cannabinoid pharmacopoeia. As currently formulated, parenteral injection of dexanabinol is required, and it may not possess the multi-modality efficacy of Cannabis Based Medicine Extracts.

### ***HU-308***

Another agent emerging from the research of Raphael Mechoulam's laboratories in Israel is HU-308, a synthetic and specific CB<sub>2</sub> agonist lacking cannabinoid behavioral effects in laboratory animals (Hanus et al. 1999). Observed activities of this agent include inhibition of forskolin-stimulated cyclic AMP production, blood pressure reduction, inhibition of defecation, and production of peripheral analgesia with anti-inflammatory effects. Further testing may demonstrate an important therapeutic role for this agent.

### ***SR141716 (RIMONABANT®)***

Heretofore, our discussion has centered on cannabinoid agonists or analogues. However, given the profile of cannabinoid stimulation with its decremental effects on short-term memory acquisition and stimulation of hunger, it was expected that efforts would be mounted to clinically harness antagonistic cannabinoid effects. SR141716, dubbed Rimonabant®, is a potent CB<sub>1</sub>-antagonist or inverse agonist used extensively in laboratory studies. It has demonstrated anti-obesity effects in mice (Ravinet Trillou et al. 2003), and is currently in human clinical trials. Preliminary results (Le Fur et al. 2001) demonstrate reduction of hunger and food intake in obese male subjects in the short term, and weight reduction in the long term, with a reportedly benign adverse effect profile. Certainly, caveats are necessary, and one might expect the emergence of depression and hyperalgesic states in patients taking this agent, such as migraine and fibromyalgia. Additionally, hypervigilance will be necessary in administering such a drug to women of child-bearing age, as SR141716 has profound effects on neonatal feeding and growth (Fride 2002).

### **NEW INDICATIONS FOR CANNABINOID PHARMACEUTICALS**

Emerging concepts have demonstrated the key role that endocannabinoids play in regulation of pain (Pertwee 2001), hormonal regulation and fertility (Bari et al. 2002), hunger (Fride 2002) and gastrointestinal function (Pertwee 2001), and even regulation of memory (Hampson and Deadwyler 2000), and proper extinction of aversive events (Marsicano et al. 2002).

Some of these concepts have recently been reviewed (Baker et al. 2003). In particular, the authors distinguish that cannabis and endocannabinoids may demonstrate an impairment threshold if too elevated, a range of normal function below which a deficit threshold is breached. This seems to be a simple and universal concept: for every neurotransmitter or neuromodulatory agent, there may be too much or too little, with corresponding clinical pathophysiological sequelae. With respect to endocannabinoids, this concept has been insufficiently explored. Previously, this author has postulated the likelihood of clinical endogenous cannabinoid deficiency diseases (CECDD) (Russo 2001, 2001), including migraine, fibromyalgia, idiopathic bowel syndrome (IBS, “spastic colon”) and possible even psychiatric conditions, such as obsessive-compulsive disorder. In light of newer information, one may posit the addition of many other disease conditions that are seemingly unresponsive to pharmacotherapy with other agents that do not influence the endocannabinoid system: causalgia and allodynia as in brachial plexus neuropathy and phantom limb pain, post-traumatic stress disorder (PTSD), bipolar disease (Grinspoon and Bakalar 1998), dysmenorrhea (Russo 2002), hyperemesis gravidarum (Russo 2002; Curry 2002), unexplained fetal wastage, glaucoma (Jarvinen, Pate, and Laine 2002), and many others.

In the area of pain, it may be the case that we need to renew a therapeutic maneuver of the 19th century (reviewed in (Russo 2002), and supported in (Cichewicz and Welch 2002)) by combining cannabinoids and opioids, particularly post-operatively or in cases of major trauma, thereby producing analgesic synergy, reducing dosages, and adverse effect profiles with respect to opiate-induced nausea, constipation and dysphoria.

Recently, a new indication for cannabinoid manipulation has been claimed, that of improved night vision. Based on simultaneous ethnobotanical claims of fisherman that cannabis stimulated their ability to see in the dark (West 1991; Merzouki and Molero Mesa 1999) in Jamaica

and Morocco, respectively, a two-pronged pilot study was launched (Russo et al. 2003). In a double-blind controlled dosage escalation study with THC as Marinol<sup>®</sup>, improvement in scotopic sensitivity was noted in one subject, while in a subsequent field study with smoked *kif* (*Cannabis sativa/Nicotiana rustica* mixture) in three subjects, improvement in both dark adaptation and scotopic sensitivity thresholds were noted with the SST-1 Scotopic Sensitivity Tester (Peters, Locke, and Birch 2000). Given the relative paucity of CB<sub>1</sub> receptors in the striate cortex (Glass, Dragunow, and Faull 1997), and their particular density in rod spherules (Straiker et al. 1999), this phenomenon seems to be of retinal, rather than cortical origin. This is further supported by anecdotal claims that cannabis improves vision in retinitis pigmentosa (Arnold 1998). Based on these findings, more formal studies of RP with fully objective measures such as electroretinography seem warranted. Given the neuroprotective and antioxidant effects of cannabis and cannabinoids, extension of therapy to senile macular degeneration appears most promising.

### CANNABINOIDS AND NEUROPROTECTION

In light of recent demonstration of the ability of THC and CBD to prevent cell death from glutamate toxicity (Hampson et al. 1998), a whole host of new therapeutic applications gain more than theoretical support beyond the current studies of stroke and closed head injury discussed in relation to dexamabinol. Therapeutic claims for cannabis in amyotrophic lateral sclerosis (ALS) have been advanced in a single case study (Carter and Rosen 2001), and it may prove to be that neurodegeneration may be diminished or arrested in this disorder, Huntington disease (Glass 2001), Parkinson disease (Sieradzan et al. 2001), Alzheimer disease (Volicer et al. 1997), and others. Neuroprotection is a valuable effect, as well, in treatment of seizure disorders (Cunha et al. 1980; Carlini and Cunha 1981; Wallace, Martin, and DeLorenzo 2002). The role of cannabis therapeutics in HIV encephalopathy and slow virus (prion) diseases (Bovine Spongiform Encephalopathy (BSE) or “mad cow disease,” Creutzfeldt-Jakob disease, etc.) deserves exploration based on these preliminary findings.

Emerging concepts in psychiatry support that depression is not merely attributable to deficiencies of serotonin, norepinephrine or dopamine (Delgado and Moreno 1999), but rather, may represent a disorder of neuroplasticity suggesting the desirability to employ neuroprotective

agents. An extensive history of such use over the last 4000 years (Russo 2001), coupled with this new information, lends credence to the hypothesis. With their unique pharmacological profiles, CBMEs deserve an effort in clinical trials.

### ***SPASMODIC DISORDERS***

The current information supporting muscle relaxant benefits of cannabis and cannabinoids in MS and spinal cord injury is extremely compelling. Mining the data of the past (O'Shaughnessy 1838-1840; Christison 1851; Reynolds 1868, 1890), one may wonder anew about the role of cannabinoid therapeutics in disorders such as tetanus, hiccup (Gilson and Busalacchi 1998), stiff man syndrome, the various periodic paralyses, and dystonic disorders such as torticollis, dystonia musculorum deformans, stuttering, and writer's cramp.

### ***FORBIDDEN TERRITORIES***

#### ***Obstetrics and Gynecology***

This topic has been recently reviewed at length (Russo 2002; Russo, Dreher, and Mathre 2003). Cannabis has been employed for millennia for a variety of related ills. Drugs are rightly eschewed when possible in pregnancy, but cases arise frequently wherein such treatment is necessary, even to save the life of mother and child. Close scrutiny of the literature supports the relative safety of cannabis in such applications, and particularly in episodic use, it is highly likely that the cost-benefit ratio in serious disorders is quite acceptable. Controlled studies of dysmenorrhea, hyperemesis gravidarum and other disorders with cannabis-extracts and medicines should be advanced.

#### ***Cannabinoid Medicines in Pediatrics***

It is clear that cannabis and cannabinoids hold promise in for many intractable and desperate pediatric conditions, although this concept may be anathema to some.

Although it is frequently the butt of jokes, no one who has not been the parent of an affected infant can truly conceive of the stress and disturbance engendered by infantile colic. A developmental disorder ap-

pearing most often between two weeks and three months of life, this poorly understood syndrome produces nightly bouts of inconsolable crying and apparent abdominal cramping pain. Myriad remedies aimed at every imaginable neurotransmitter system of brain and gut tend to fail to stem its ravages. Perhaps infantile colic is another developmental clinical endogenous cannabinoid deficiency disorder. With its anti-spasmodic, analgesic, anti-anxiety and soporific attributes, a THC:CBD cannabis extract holds promise where other agents have disappointed, and if so, countless new parents may be thankful.

Another possible pediatric indication for cannabis-based medicines is cystic fibrosis. In a recent study (Fride 2002), an extremely compelling and well-conceived rationale for cannabis treatment was outlined that could vastly improve the clinical condition and well-being of affected children. Similar benefits might accrue to other serious failure-to-thrive states.

Cannabis medicines have already demonstrated remarkable success in allaying nausea and vomiting in children undergoing cancer chemotherapy (Abrahamov and Mechoulam 1995). Unfortunately, this study has been largely ignored, rather than being duplicated and extended. Any possible moral objection to such treatment holds no weight when the alternative is severe suffering and even death of a child. The recent report of cannabidiol (CBD) inhibition of glioma cell growth by promotion of apoptosis independent of cannabinoid and vanilloid receptor activity (Vaccani, Massi, and Parolaro 2003), should convince all but the most hardened detractors.

A less lethal, but yet still compelling potential indication is childhood asthma. The advent of new delivery devices for cannabis medicines discussed in this volume, combining bronchodilation, with modulation of leukotrienes and other mediators of inflammation offer unique benefits to this disorder.

Finally, the area of child psychiatry deserves additional consideration. A recent book, *Jeffrey's Journey: A Determined Mother's Battle for Medical Marijuana for Her Son* (Jeffries and Jeffries 2003), documents the case study of a young man who failed every conceivable psychopharmacological agent to control his anger and other psychopathology. Only oral cannabis worked, preventing his imminent institutionalization, and allowing a return to a semblance of normal life.

This author, in his practice of child and adult neurology, has heard dozens of unsolicited testimonials to the benefits of cannabis in attention-deficit hyperactivity disorder (ADHD), supporting available anecdotal accounts (Grinspoon and Bakalar 1997). Although the idea of



using cannabis-based medicines for this indication may seem surprising to most experts, controlled trials of cannabis medicines for children with ADHD seem clearly indicated, particularly in view of the controversies and side effects of existing psychotropic medications. Extension of the concept to other difficult disorders of obscure pathophysiology such as autistic spectrum and Asperger disorders may be warranted. If and when cannabis establishes its efficacy in pediatric diseases, it shall have achieved a fair measure of redemption from the derision it has elicited during the past century.

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